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(71) Applicant *(for all designated States except US)*: RIKER LABORATORIES, INC. [US/US]; 19901 Nordhoff Street, Northridge, CA 91324 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)* : JINKS, Philip, Anthony [GB/GB]; 37 Glebe Close, Mountsorrel, Leicestershire (GB). BELL, Alexander [GB/GB]; 15 Marton Road, Chilwell, Beeston, Nottinghamshire (GB). FISCHER, Franz, Xaver [AT/CH]; Hoehenstrasse 27, CH-4125 Riehen (CH).

(74) Agent: LLOYD WISE, TREGEAR & CO.; Norman House, 105-109 Strand, London WC2R OAE (GB).

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(54) Title: DRUG-CONTAINING CHLOROFLUOROCARBON AEROSOL PROPELLENT FORMULATIONS

(57) Abstract

Complete dissolution of a wide range of drugs in chlorofluorocarbon aerosol propellents is achieved by the presence of glycerol phosphatides, preferably phosphatidylcholine.

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DRUG-CONTAINING CHLOROFLUOROCARBON AEROSOL PROPELLENT FORMULATIONS

This invention relates to medicinal aerosol formulations and in particular to drug-containing chlorofluorocarbon aerosol propellent formulations for topical or for endopulmonary or nasal inhalation administration.

Medicinal aerosol formulations generally contain a mixture of chlorofluorocarbons, e.g. trichloromonofluoromethane (Propellent 11), dichlorotetrafluoroethane (Propellent 114) and dichlorodifluoromethane (Propellent 12). The drug is either present as a solution in the aerosol formulation or as a dispersion of fine particles. For endopulmonary or nasal inhalation, particles predominantly in the size range 2 to 5 microns are required.

There are very few drugs which can be solubilised in chlorofluorocarbon aerosol propellents alone. Generally, it is necessary to utilise a polar co-solvent, such as ethanol, in order to achieve solubilisation of the drug. However, the resulting solutions can be chemically unstable due to reaction between the co-solvent and the drug or the co-solvent and the propellent system.

Furthermore, when large proportions of co-solvent, e.g. ethanol, are required to achieve dissolution of the drug, the resulting spray droplet size may be too large for certain applications, in particular, endopulmonary inhalation therapy.

Suspension of drug in aerosol propellents is achieved by pulverising the drug into the desired particle size range and thereafter suspending the particles in propellents with the aid of a surfactant. The disadvantages of this technique are that drug particles may agglomerate, grow in size or become adsorbed onto the surface of the container in which the formulations are stored prior to dispensing. Furthermore, it is necessary to agitate the product prior to use in order to ensure dispersion of the formulation and uniformity of dosage.

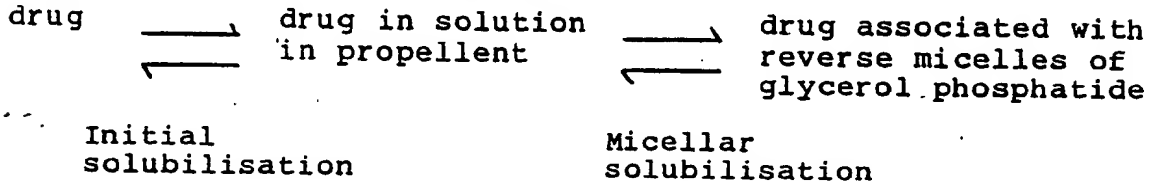
The present invention provides an alternative technique for incorporating drugs into chlorofluorocarbon aerosol propellents.

Therefore according to the invention there is provided an aerosol formulation comprising one or more chlorofluorocarbon aerosol propellents, a glycerol phosphatide and a drug, the drug being dissolved in the composition.

The glycerol phosphatide may be any one of the following compounds; phosphatidylcholine (lecithin), phosphatidylethanolamine (cephalin), phosphatidylinositol, phosphatidylserine, diphosphatidylglycerol or phosphatidic acid.

Surprisingly it has been found that glycerol phosphatides cause complete dissolution of certain drugs in chlorofluorocarbon propellents. Phosphatidylcholine (lecithin) has been utilised as a surfactant in aerosol formulations containing suspended drug particles but heretofore it has not been appreciated that this particular compound can enhance the solubility of certain drugs in chlorofluorocarbon propellents.

It has been found that drugs having at least very slight solubility in chlorofluorocarbon propellents will exhibit an enhanced solubility in the chlorofluorocarbon propellent in the presence of glycerol phosphatide. It is postulated that this enhanced solubility is attributable to drug in true solution becoming associated with reverse micelles of the glycerol phosphatide which allows further drug to dissolve in the propellent. Thus, the solubilisation process is believed to be as follows:



Whilst the compositions of the invention appear visibly to be true solutions since there is no dispersed phase apparent, they are more correctly micellar solutions.

The formulations of the invention may be prepared by forming a concentrate of glycerol phosphatide with a drug and Propellent 11. The concentrate may be formed by simple admixture with agitation and optionally under heating, e.g. 50°C, until complete dissolution of the drug has been attained. The concentrate may then be mixed with the remainder of the propellent formulation, e.g. Propellents 12 and 114.

Phosphatidylcholine is the most suitable glycerol phosphatide to use in view of its low toxicity and high drug solubilising efficacy. Phosphatidyl-choline purified from soya bean lecithin is readily available commercially and suitable grades include Epikuron 200 (Lucas-Meyer) and Lipoid S100

(Lipoid KG). Both products have a phosphatidylcholine content in excess of 95%

It has been found that certain drugs which are practically insoluble in chlorofluorocarbon propellents alone can be solubilised in the propellent/glycerol phosphatide system by the addition of a small amount of a co-solvent such as ethanol.

It is postulated that the co-solvent enhances the initial solubilisation step of the solubilisation process. Certain commercially available forms of lecithin, in addition to their phosphatidylcholine content, contain ethanol as an impurity. With compounds of this type, e.g. Lipoid S45, the ethanol may likewise enhance drug solubilisation.

Suitable drugs for use in the invention comprise those compounds which exhibit at least a very slight solubility in a chlorofluorocarbon propellent. In general, the drug will be in the form of an ester, base or free alcohol. Highly polar ionic salts of drugs are less suitable since it may not be possible to solubilise the drug in sufficient quantity even with the presence of a small amount of co-solvent.

Exemplary drugs include steroids, e.g. beclomethasone dipropionate, betamethasone dipropionate, acetate, valerate and free alcohol. Other drugs include salbutamol base, atropine base, prednisolone, formoterol base, hydrochloride, fumarate and hemisulphate.

Further suitable drugs for use with the invention include the following:

Anorectics: e.g. benzphetamine hydrochloride
chlorphentermine hydrochloride

Anti-depressents: e.g. amitriptyline hydrochloride
imipramine hydrochloride
Anti-hypertensive agents: e.g. clonidine hydrochloride
Anti-neoplastic agents: e.g. actinomycin C
Anti-cholinergic agents: atropine base
Dopaminergic agents: e.g. bromocriptine mesylate
Narocotic analgestics: e.g. buprenorphine hydrochloride
Beta-adrenergic blocking agents: e.g. propranolol hydrochloride
Corticosteroids: e.g. lacicortone, hydrocortisone, fluocinolone acetonide, triamcinolone acetonide
Prostaglandins: e.g. dinoprost trometamol
Sympathomimetics: e.g. xylometazoline hydrochloride
Tranquillisers: e.g. diazepam, lorazepam
Vitamins: e.g. folic acid, nicotinamide
Brochodilators: e.g. clenbuterol hydrochloride
bitolterol mesylate
Sex hormones: e.g. ethinyloestradiol, levonorgestrel.

The ratio of drug : glycerol phosphatide : cosolvent (if required) : chloro-fluorocarbon propellent depends upon a number of criteria:

1) The concentration of drug required in the final formulation.

2) The solubility of glycerol phosphatide in the particular blend of chlorofluorocarbon propellents.

3) The droplet size and evaporation characteristics required of the emitted spray. For inhalation purposes the optimum levels of glycerol phosphatide and Propellent 11 will be the minimum permissable levels to achieve a stable solution. Higher levels of these components

result in an increase in the droplet size of the spray upon dispensing due to a lowering of the volatility of the formulation.

4) Solubility of the drug in the propellents or propellent/co-solvent.

A wide range of propellents may be used in the formulations of the invention including:

Propellent 11 trichloromonofluoromethane
Propellent 12 dichlorodifluoromethane
Propellent 13 monochlorotrifluoromethane
Propellent 21 dichloromonofluoromethane
Propellent 22 monochlorodifluoromethane
Propellent 113 trichlorotrifluoroethane
Propellent 114 dichlorotetrafluoroethane
Propellent 115 monochloropentafluoroethane
Propellent 500 azetrope - 73.8% dichlorodifluoromethane and 26.2% 1,1-difluoroethane

In addition to chlorofluorocarbon aerosol propellent the formulations may contain other propellents, e.g. DME (dimethylether).

In general, the compositions comprising drug, glycerol phosphatide and propellent may be made within the following general weight ratios:

drug	:	glycerol phosphatide
1 to 500	:	100

glycerol phosphatide	:	propellent
0.01 to 20	:	100

For many drugs the weight ratio of drug:glycerol phosphatide will generally be in the range 1 to 30:100 and that of glycerol phosphatide:propellent in the range 0.01 to 10:100. Preferably the weight ratio of drug:glycerol phosphatide will be in the range 2 to 10:100 and that of glycerol phosphatide:propellent in the range 0.01 to 3:100.

The invention will now be illustrated by the following Examples.

Example 1

Solubilisation of beclomethasone dipropionate

		mg/ml
(a)	beclomethasone dipropionate	1
(b)	Epikuron 200	14
(c)	Propellent 11	270
(d)	Propellent 12	1080
		1365

The formulation was prepared by mixing components (a) to (c) under stirring for approximately 10 minutes at a temperature of 25°C. Thereafter the concentrate was mixed with component (d) at a temperature appropriate to the filling technique, generally in the range -60 to +20°C.
The resulting formulation was a stable solution.

Example 2

Solubilisation of salbutamol base

		mg/ml
(a)	salbutamol base	2
(b)	Epikuron 200	14
(c)	Propellent 11	339
(d)	Propellent 12	1018
		1373

The formulation was prepared as in Example 1 except that solubilisation required stirring for 30 minutes at a temperature of 50°C. A stable solution was formed.

Example 3

Solubilisation of atropine base

		mg/ml
(a)	atropine base	1
(b)	Epikuron 200	4
(c)	Propellent 11	270
(d)	Propellent 12	1080
		1355

The formulation was prepared as in Example 1 and resulted in a stable solution.

Example 4

A series of stable formulations were prepared suitable for use as concentrates in the preparation of aerosol formulations. Each concentrate comprised the following components in the weight ratio of drug : Epikuron 200 : Propellent 11 of 1:14:270. The drugs used were prednisolone, betamethasone acetate, betamethasone valerate, betamethasone dipropionate and betamethasone free alcohol.

Example 5

Solubilisation of formoterol compounds

The following formulations were prepared:

(i)

	mg/ml
formoterol hydrochloride	0.2000
ascorbyl palmitate	0.2000
Epikuron 200	2.7000
Propellent 11	341.4125
Propellent 12	1024.2375
	1368.7500

(ii)

	mg/ml
formoterol hydrochloride	0.2400
vitamin E acetate	2.7000
Epikuron 200	2.7000
Propellent 11	339.8400
Propellent 12	1019.5200
	1365.0000

(iii)

	mg/ml
formoterol hydrochloride	0.1800
Lipoid S45 Lecithin	2.7000
Propellent 11	202.0680
Propellent 12	1145.0520
	1350.0000

(iv)

	mg/ml
formoterol base	0.1600
Lipoid S45 Lecithin	2.7000
Propellent 11	202.0710
Propellent 12	1145.0690
	1350.0000

(v)

	mg/ml
formoterol hemisulphate	0.1600
Lipoid S45 Lecithin	2.7000
Propellent 11	202.0710
Propellent 12	1145.0690
	1350.0000

(vi)

	mg/ml
formoterol fumarate	0.2400
vitamin E acetate	2.7000
Epikuron 200	2.7000
Propellent 11	339.8400
Propellent 12	1019.5200
	1365.0000

(vii)

	mg/ml
formoterol fumarate	0.2400
Epikuron 200	2.7000
Propellent 11	340.5150
Propellent 12	1021.5450
	1365.0000

Vitamin E acetate and ascorbyl palmitate were included as antioxidants and did not impair the physical characteristics of the solutions.

The formulations were prepared by mixing the drug, surfactant, Propellent 11 and antioxidant (when present) under stirring for up to 6 hours at a temperature of 45 to 50°C. Thereafter the resulting solution was mixed with Propellent 12 at a temperature appropriate to the filling method to produce a solution.

Example 6

A series of stable formulations were prepared suitable for use as concentrates in the preparation of aerosol formulations. Each concentrate comprised drug, Lipoid S100 and Propellent 11 in the weight ratio of 1:7:135. The drugs used were:

Diazepam
Lorazepam
propranolol hydrochloride
hydrocortisone
fluocinolone acetonide
triamcinolone acetonide

Clear stable solutions resulted in all cases. When matching formulations were prepared omitting Lipoid S100 each drug remained in suspension.

Example 7

Use of co-solvent to aid solubilisation

A formulation was prepared consisting of xylometazoline hydrochloride, Lipoid S100 and Propellent 11 in the weight ratio 1:7:135. A matching formulation was prepared in which the Lipoid S100 was omitted. After agitation and heating at 50°C for four hours a considerable amount of drug remained in suspension, in both formulations. Ethanol 4% by weight was then added to both formulations. After 15 minutes the formulation containing Lipoid S100 was a clear solution. There was no apparent change in the formulation in which Lipoid S100 was omitted. This

result indicates the efficiency of a small amount of co-solvent in promoting the initial solubilisation step of the phospholipid solubilisation process.

Example 8

Aerosol formulations containing Diazepam

The following formulations were prepared:

		mg/ml	
(a)	Diazepam	20	
	Lipoid S100	7	
	Propellent 11	370.5	30%
	Propellent 12	864.5	70%
		1262.0	

		mg/ml	
(b)	Diazepam	20	
	Lipoid S100	7	
	Propellent 11	264.3	30%
	DME	616.7	70%
		908.0	

The formulations were physically stable solutions.

Example 9

Use of Propellents 113 and 115 in solubilised formulations

The following formulation was prepared:

	mg/ml
Lorazepam	1.87
Lipoid S100	13.09
Propellent 113	252.59

Propellent 115	126.29
Propellent 22	884.06
	1277.90

Dissolution of the concentrate containing Lorazepam, Lipoid S100 and Propellent 113 was achieved by heating at 50°C for 10 minutes. Propellent 115 and Propellent 22 were then combined with the concentrate and a physically stable solution resulted.

Example 10

Use of Propellent 500 (Azeotrope) in solubilised formulation

The following formulation was prepared:

	mg/ml
Propranolol HCl	3.02
Lipoid S100	21.14
Propellent 11	407.65
Propellent 500	951.19
	1383.00

A physically stable solution formulation resulted.

Example 11

Solubilisation of bitolterol mesylate

The following formulations were prepared:

	mg/ml	mg/ml
bitolterol mesylate	4.00	8.00
Lipoid S100	10.00	20.00
Propellent 11	201.30	199.20
Propellent 12	1140.70	1128.80
	1356.00	1356.00

Solubilisation occurred readily in the Propellent 11/ lecithin/drug concentrates at room temperature. Both solution formulations were stable at -60°C enabling the cold filling technique to be employed when preparing pressurised dispensing packs.

Example 12

Solubilisation of Lacicortone

The following formulations were prepared:

	(a) mg/ml	(b) mg/ml
Lacicortone	2.00	5.00
Lipoid S100	7.00	14.00
Propellent 11	271.20	408.60
Propellent 12	1084.80	953.40
	1365.00	1381.00

Solubilisation occurred readily in the Propellent 11/ lecithin/drug concentrates at room temperature. Formulation (a) was stable at -60°C and Formulation (b) was stable at -50°C enabling the cold filling technique to be employed when preparing pressurised dispensing packs.

Example 13

Use of glycerol phosphatides

The following formulations were prepared:

	parts by weight
beclomethasone dipropionate	1
phosphatidyl serine	14
Propellent 11	270

beclomethasone dipropionate	1
phosphatidyl ethanolamine	14
Propellent 11	270
salbutamol base	1
phosphatidyl serine	14
Propellent 11	270
salbutamol base	1
phosphatidyl ethanolamine	14
Propellent 11	270

Each formulation was a stable clear solution suitable for use as a concentrate in the preparation of aerosol formulations.

CLAIMS:

1. An aerosol formulation comprising one or more chlorofluorocarbon aerosol propellents, glycerol phosphatide and a drug, the drug being dissolved in the composition.

2. A formulation as claimed in Claim 1, in which the glycerol phosphatide is selected from phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, diphosphatidylglycerol, phosphatidic acid and mixtures thereof.

3. A formulation as claimed in Claim 2, in which the glycerol phosphatide is phosphatidylcholine.

4. A formulation as claimed in any preceding claim, in which the glycerol phosphatide is purified.

5. A formulation as claimed in any one of Claims 1 to 4, which comprises Propellent 11, glycerol phosphatide and a drug.

6. A formulation as claimed in any preceding claim, in which the ratio of glycerol phosphatide to Propellent 11 is 0.01 to 20:100.

7. A formulation as claimed in any preceding claim, in which the ratio of glycerol phosphatide to Propellent 11 is 0.01 to 10:100.

8. A formulation as claimed in any preceding claim, in which the ratio of glycerol phosphatide to Propellent 11 is 0.01 to 3:100.

9. A formulation as claimed in any preceding claim, which comprises one or more of propellents selected from Propellents 11, 12, 13, 21, 22, 113, 114, 115 and 500.

10. A formulation as claimed in any preceding claim, in which the ratio of drug to glycerol phosphatide is 1 to 500:100.

11. A formulation as claimed in any preceding claim, in which the ratio of drug to glycerol phosphatide is 1 to 30:100.

12. A formulation as claimed in any preceding claim, in which the ratio of drug to glycerol phosphatide is 2 to 10:100.

13. A formulation as claimed in any preceding claim, which additionally comprises a small amount of a co-solvent to enhance the solubilisation process.

14. A formulation as claimed in any preceding claim, in which the drug is selected from beclomethasone dipropionate, betamethasone dipropionate, acetate, valerate and base thereof, salbutamol base, atropine base and prednisolone.

15. A formulation as claimed in any one of Claims 1 to 13, in which the drug is selected from formoterol base, hydrochloride, hemisulphate and fumarate.

16. A formulation as claimed in any one of Claims 1 to 13, in which the drug is selected from diazepam, lorazepam, propranolol hydrochloride, hydrocortisone, fluocinolone acetonide, triamcinolone acetonide, xylometazoline hydrochloride, bitolterol mesylate and lacicortone.

17. A pressurised aerosol pack filled with a formulation as claimed in any preceding claim.

18. A method of solubilising a drug having slight solubility in chlorofluorocarbon aerosol propellents which comprises mixing said drug in a chlorofluorocarbon propellent in the presence of an effective amount of a glycerol phosphatide.

19. A method as claimed in Claim 18, in which the glycerol phosphatide is selected from phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, diphosphatidylglycerol and phosphatidic acid.

20. A method as claimed in Claim 18, in which the glycerol phosphatide is phosphatidylcholine

21. A method as claimed in any one of Claims 18 to 20, in which the glycerol phosphatide is purified.

22. A method as claimed in any one of Claims 18 to 19, which comprises Propellent 11, glycerol phosphatide and a drug and the admixture is conducted under stirring.

23. A method as claimed in Claim 21, in which the ratio of glycerol phosphatide to Propellent 11 is 0.01 to 20:100.

24. A method as claimed in any one of Claims 19 to 21, which comprises one or more of propellents selected from Propellents 11, 12, 13, 21, 22, 113, 114, 115 and 500.

25. A method as claimed in any one of Claims 18 to 24, which additionally comprises a small amount of a co-solvent to enhance the solubilisation process.

26. A method as claimed in any one of Claims 18 to 25, in which the drug is selected from beclomethasone dipropionate, betamethasone dipropionate, acetate, valerate and base thereof, salbutamol base, atropine base, and prednisolone.

27. A method as claimed in any one of Claims 18 to 25, in which the drug is selected from formoterol base, hydrochloride, hemisulphate and fumarate.

28. A method as claimed in any one of Claims 18 to 25, in which the drug is selected from diazepam, lorazepam, propranolol hydrochloride, hydrocortisone, fluocinolone acetonide, triamcinolone acetonide, xylometazoline hydrochloride, bitolterol mesylate and lacicortone.

29. A process for solubilising a drug having slight solubility in chlorofluorocarbon aerosol propellent which comprises using an effective amount of glycerol phosphatide.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 86/00001

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 9/72; A 61 K 9/12; A 61 K 47/00

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K 9/00 A 61 K 7/00 A 61 K 31/00 A 61 K 47/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	GB, A, 993702 (TAKEDA) 2 June 1965, see claims; page 1, lines 45-70; page 2, lines 3-45; example 1 --	1-13,16-25, 28,29
A	GB, A, 2001334 (FISONS) 31 January 1979, see claims --	1-3,14,16
A	US, A, 3551558 (TAKEDA et al.) 29 December 1970, see claim --	1-3
A	DE, A, 2802113 (SANDOZ) 26 July 1979, see examples 2,6	17,18

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17th March 1986	10 APR 1986
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. VAN MOL

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/GB 86/00001 (SA 11756)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 02/04/86

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A- 993702		None		
GB-A- 2001334	31/01/79	BE-A-	869055	17/01/79
		NL-A-	7807625	23/01/79
		FR-A,B	2397833	16/02/79
		DE-A-	2831419	01/02/79
		JP-A-	54035209	15/03/79
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		SE-B-	443087	17/02/86
US-A- 3551558	29/12/70	None		
DE-A- 2802113	26/07/79	None		